EC regeneration in cerebrovascular ischemia: role of NO

Grant Award Details

EC regeneration in cerebrovascular ischemia: role of NO

Grant Type: SEED Grant

Grant Number: RS1-00183

Investigator:

Name:	John Cooke
Institution:	Stanford University
Type:	PI

Disease Focus: Vascular Disease

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $476,995

Status: Closed

Grant Application Details

Application Title: EC regeneration in cerebrovascular ischemia: role of NO

Public Abstract:

Stroke is the third leading cause of death and the leading cause of disability in this country, affecting about 650,000 people in the US each year. Currently approved therapies for stroke are directed toward acutely restoring blood flow (using drugs that break up clot). A new approach is to use stem cells to regenerate portions of the brain that are damaged in a stroke. Stem cells can be obtained from adult individuals, or from embryos. Studies using adult stem cells have shown that only a small fraction of these cells are capable of transforming into brain cells. Another problem is that in patients with stroke, many different types of brain cells must be replaced. Furthermore, the replacement cells must reconstitute the normal architecture of the lost brain. Additionally, the stem cells must overcome the hostile metabolic milieu in the ischemic brain, which includes poor blood flow, as well as the adverse metabolic environment that caused the stroke in the first place (eg. high blood sugar, high cholesterol, high blood pressure).

So in this proposal we are taking a different approach. We will develop methods to make blood vessels using human embryonic stem cells (HESC). HESC derived blood vessel cells will be injected into rats that have had a surgically-induced stroke. We will determine if the HESC-derived vascular cells find their way to the area of poor blood flow. We will determine if these cells survive and if they generate new blood vessels.

In other works, rather than attempting to provide stem cells that will develop into complex brain tissue after stroke, we intend to first restore the brain vessels in the area of the stroke. We hypothesize that "if we build the road, they will come", ie. the restoration of the brain vessels will enhance survival of brain tissue in areas of poor flow, and may induce repair of the injured area, by encouraging neighboring nerve cells to migrate into the area.

Furthermore, we plan to genetically engineer the HESCs to make them hardier. The area of stroke in the brain is a hostile environment for cells. One of the factors that mediates the adverse metabolic effects is a substance called ADMA (asymmetric dimethylarginine). We will engineer HESC that are more able to handle this substance, and determine if that genetic modification gives the HESC a better chance of surviving and forming blood vessels.

This proposal will provide insights into the use of human embryonic stem cells (HESC) for regenerating the injured brain after a stroke.

Statement of Benefit to California:

Every 45 seconds, someone in California has a stroke. Stroke is the third leading cause of death and the leading cause of disability in California. Each year, stroke kills more than twice as many Californian women as does breast cancer. Currently approved therapies for stroke are limited. The only FDA approved therapy that is directed toward stroke is thrombolysis (using drugs that break up clot). New approaches are needed.

A novel approach is to use stem cells to regenerate portions of the brain that are damaged in a stroke. Stem cells can be obtained from adult individuals, or from embryos. Studies using adult stem cells have shown that only a small fraction of these cells are capable of transforming into brain cells. Another problem is that in patients with stroke, many different types of brain cells must be replaced. Furthermore, the replacement cells must reconstitute the normal architecture of the lost brain. Additionally, the stem cells must overcome the hostile metabolic milieu in the ischemic brain, which includes poor blood flow, as well as the adverse metabolic environment that caused the stroke in the first place (eg. high blood sugar, high cholesterol, high blood pressure).

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This proposal will provide insights into the use of human embryonic stem cells (HESC) for regenerating the injured brain after a stroke. These insights are likely to generate new intellectual property. The principal investigator has a track record of translational research. Our laboratory has generated fundamental biological insights that have been applied to disease models, and ultimately used to develop new therapies. The patents from our laboratory have had a high rate of licensure. From these patents there are now products in the pipeline, several in clinical trials, and one on the market. To summarize, support of this proposal is likely to generate fundamental new insights into the biology of vascular cells derived from human embryonic stem cells, and may lead to new therapeutic avenues that are desperately needed for stroke.
